IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Jessie L.S.-Au, *et al*.
Serial No.	:	10/807,620
Filed:	:	March 24, 2004
For:	:	Methods And Compositions To Determine The Chemosensitizing Dose Of Suramin Used In Combination Therapy
TC/AU	:	1614
Examiner	:	James D. Anderson
Attorney Docket No.	:	TNI 2-011

BOARD OF PATENT APPEALS AND INTERFERENCES
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

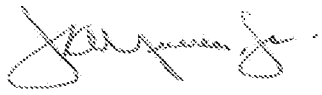
APPELLANTS' BRIEF ON APPEAL

Sir:

Responsive to a Communication mailed January 5, 2009, submitted herewith is Appellant's Brief on Appeal as prescribed in 37 C.F.R. § 41.31. Reversal of the primary examiner's rejection of the appealed claims and their allowance is respectfully requested.

The requisite fee of $270.00 as required in 37 C.F.R. § 1.17(c) is submitted herewith. Any additional payments that may be required should be charged to Deposit Account No. 13-4830.

Respectfully submitted,



Date: 26 August 2009

Jerry K. Mueller, Jr.
Reg. No. 27,576
MUELLER SMITH & OKULEY, LLC
Mueller-Smith Building
7700 Rivers Edge Drive
Columbus, Ohio 43235-1355
tel.: 614-436-0600
fax: 614-436-0057
email: *smueller@muellersmith.com*

Real Party in Interest

The appealed application has not been assigned; however, Optimum Therapeutics, LLC has commercial rights in the application.

Related Appeals and Interferences

There are no related appeals or interferences known to Applicants, their legal representatives, or assignee, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

Status of Claims

Twenty-six claims were submitted with the application as originally filed.

An Office Action was mailed on January 9, 2007 containing a three-way restriction requirement. In a response filed on February 6, 2007, Applicants elected the Group III claims 22-24, 26, and new claims 27-33. Claim 25 was cancelled. All other claims were withdrawn from prosecution.

An Office Action was mailed on June 6, 2007 rejecting claims 22-24 and 26-33. Applicants filed a response on September 10, 2007, canceling claims 23-25 and 29, and adding new claim 34.

An Office Action was mailed on December 12, 2007 rejecting claims 22, 26-28, and 30-34. Applicants filed a response on March 6, 2008, that included a declaration from co-inventor Dr. Jessie L.-S. Au.

An Advisory Action was mailed on April 9, 2008 entering the March 6, 2008 response with declaration, but maintaining the rejection of the claims.

Applicants filed a Pre-Appeal Brief Request for Review on June 17, 2008 with a Notice of Appeal. A Notice of Panel Decision From Pre-Appeal Brief Review was mailed on July 11, 2008 reopening prosecution, withdrawing the finality of the December 12, 2007 Office action, and deeming the Notice of Appeal Moot. Claims 22, 26-28, and 30-34 again were rejected. Applicants filed an amendment on October 15, 2008 amending claim 22 and canceling claim 31.

An Office Action was mailed on January 5, 2009 rejecting claims 22, 26-28, 30, and 32-34. Applicants filed a response on July 1, 2009. The instant Notice of Appeal was filed on July 6, 2009.

Status of Amendments

All of the amendments submitted by Appellants have been entered.

Summary of the Claimed Subject Matter

The claims are directed to a kit for carrying out the combined administration of suramin with a cytotoxic agent (see claim 1). In particular, the kit includes suramin in a pharmaceutical carrier, a specific cytotoxic agent, and instructions for therapeutic use of said suramin in combination with said cytotoxic agent(s) in one or more of inhibiting growth, proliferation of tumor cells, or inducing killing of tumor cells. The instructions include the steps of administering suramin in a required dose to establish a low circulating concentration of suramin of below about 200 μM and administering the chemotherapeutic agent when the circulating concentration of suramin in the patient is below about 200 μM.

The requisite dose of suramin is determined by the squared value of the body surface area of the patient, the elapsed time in days since initiation of the last suramin treatment, and a nomogram that shows the dose according to the parameters of squared value of the body surface area of the patient and the elapsed time in days since initiation of the last suramin treatment. The nomogram provides a Factor that, along with the squared value of the body surface area of the patient and the elapsed time in days since initiation of the last suramin treatment, are inputted into disclosed formulas: equations 15 and 16.

The nomogram disclosed in the appealed application is a simple and practical way to calculate a suramin dose in individual patients that will yield a narrow range of plasma concentrations between 10 to 50 μM (equal to about 14 to 71 μg/ml; see claim 28) over a defined duration of 48 hours (see claim 32), in situations where suramin is given with a cytotoxic agent. As the therapeutic benefits of suramin are observed only at these conditions and are lost at higher concentrations, a physician must have the means to determine the suramin dose that would yield these concentrations. The 48-hour duration reflects the duration that the cytotoxic is also present in the body at an active concentration, since most drugs have a half-life of about or less than 16 hours and since most of the drug dose are eliminated after three half-lives (*i.e.*, 3 times 16 hours). For most drugs, choosing the proper dose is a relatively routine and easy task. For example, most chemotherapy agents are given at a fixed frequency and at a fixed dose, because most agents have plasma half-lives of several hours and are eliminated from the body within days, and, therefore, will not show significant accumulation in the body by the time the next dose is administered, usually in 7 or 21 days.

However, this general practice does not apply to suramin, due to its unusual pharmacokinetic characteristics. First, the disposition of low and non-cytotoxic doses of suramin in patients shows a substantial inter-subject variability (180%), indicating that the same dose of suramin will not result in the same, desired plasma concentration in all patients. In fact, different patients require doses of up to 5-fold different size (Chen, *Pharm. Res.*, 23, 1265,

2006). Second, suramin has an unusually slow elimination from the body with a half-life of about 10 days, indicating that a significant residual amount will remain in the body at the time of the next treatment (*e.g.*, about 25% of the dose remaining in 20 days for a half-life of 10 days). Third, unexpected changes in treatment frequency or time intervals between treatment cycles are fairly common in cancer chemotherapy. These changes will affect the amount of residual drug and, therefore, introduce uncertainty on deciding on the proper dose. If the dose in the subsequent treatment exceeds the amount that has been eliminated, drug accumulation will occur and will cause the plasma concentrations to increase, *e.g.*, to levels where suramin is not effective. Conversely, an insufficient dose will yield ineffective concentrations. Hence, a method or composition to take into account the various patient characteristics and the time interval between treatments, so that the patient is given the proper suramin dose, is absolutely required to achieve the benefits of suramin sensitization.

As indicated in the appealed application and in Applicants' publication (Chen, 2006), the development and validation of the nomogram method required extensive research, and yielded surprising and unexpected results that either cannot be anticipated from the prior art, or contradicts the prior art. The nomogram development was a multi-step process, as stated in (Chen, 2006), page 1266: 2, last ¶:

> first, we used the pharmacokinetics results in the first cohort of six phase I patients to determine the duration that covered >90% of paclitaxel/carboplatin AUC, with the goal of maintaining the plasma suramin concentrations at between 10 and 50 μM over this duration. This led to adjustments in the suramin regimen; administering suramin in two split doses yielded the target concentrations over 48 hour in the second cohort of six patients. The pharmacokinetics results of these 12 patients were then used with PPK [population-based pharmacokinetic] analysis to derive suramin dosing equations, which were then used to predict the dose in three additional patients. Through retrospective and prospective analyses of the precision and accuracy of the PPK based dosing equations, a correction factor was identified and used to derive a dosing nomogram. The predictive power of the nomogram was evaluated in 47 phase II patients."

As described in the application (Example IV), during the PPK phase of the nomogram development, 10 potential covariates were evaluated. One of these was patient gender. The initial results in a small number of patients suggested that the dose was affected by patient gender. However, further evaluation in large numbers of patients indicated that the gender-related difference in dose requirement was so small that it could be ignored. Another potential covariates was creatinine clearance, which was expected to be strongly correlated with suramin clearance. This is because earlier literature reported renal elimination as the primary route of clearance of suramin (Collins, *J. Clin. Pharmacol.*, 26, 22, 1986; Piscitelli, *Pharmacotherapy*, 17, 431, 1997). Motzer, *et al*. ("Phase II Trial of Suramin in Patients with Advanced Renal Cell

Carcinoma: Treatment Results, Pharmacokinetics, and Tumor Growth Factor Expression" *Can Res* **53**, 5775-5779, October 15, 1992) were under this same impression, as evidenced by their statement on page 5776, column 1, Introduction: "The pharmacokinetics of suramin include ..... predominantly renal elimination, ...". During further evaluation, creatinine clearance turned out not to be a significant predictor of PPK parameters. Applicants investigated this apparent discrepancy in a study in 38 patients, and determined that the renal clearance of suramin in human patients was surprisingly low, accounting for only approximately 10% of the total clearance. Another surprising finding was that body surface area (BSA) was a less accurate predictor of dose requirement than its squared value, BSA^2. This was surprising, because many anticancer agents are administered based on body surface area, while a dose requirement based on BSA^2 is unknown to Applicants and certainly extremely uncommon. Applicants further devised new methodologies for some of the steps in the nomogram development process. For example, no established method was available to optimize accuracy of the predicted dose. Applicants accomplished this task by using computer simulations to identify the "ideal dose" that would give the precisely desired plasma concentration at 48 hours. A comparison of this "ideal dose: with the actual results in patients led to the introduction of a correction factor that improved the accuracy of the nomogram predictions by 12%. The above composite findings were then used to develop the suramin dosing nomogram. The innovativeness of the nomogram is indicated by its success in finding the proper suramin dose to maintain the desired plasma concentrations in 94% of treatments, in spite of the substantial inter-patient variability (180%). This level of variability means it will be impossible to predict how a patient will react to a suramin dose, implying that, absent the nomogram, a physician or a pharmacist will not be able to determine the proper suramin dose for a patient without undue burden of extensive experimentation (see Dr. Jessie Au's declaration dated March 6, 2008).

In summary, the above shows that extensive, additional research was necessary to overcome or correct the deficiencies or misunderstanding in the art. As pointed out in Dr. Au's declaration, the amount of work involved in the development and validation of the nomogram is far beyond the standard of obviousness.

Claim 22 is directed to a kit that includes suramin (see p. 5, ll. 20-32); a cytotoxic agent (*id*; p. 13, l. 11 bridging p. 14, l. 15); and instructions for use (see, generally, p. 30, l. 15 bridging p. 34, l. 8; and original claim 22, *et seq*.). The list of cytotoxic agents in claim 26 are disclosed at p. 13, l. 11 bridging p. 14, l. 15). The suramin dose in claim 27 is discussed generally in the application at p. 5, l. 20 bridging p. 6, l. 12; and original claim 2). The suramin dose range in claim 28 is discussed in the application also at p. 5, l. 22. The suramin dose range and time frame in claim 32 is discussed in the application also at p. 6, ll. 5-6 and 8-9. The suramin doses

and sequence of administration in claim 34 is discussed generally at p. 7, l. 30 bridging p 8., l 2; and p. 11, ll. 3-4.

Grounds of Rejection to be Reviewed on Appeal

Appealed claims 22, 26-28, and 30, and 32-34 stand finally rejected under the provisions of 33 U.S.C. § 103(a) as being obvious over Agyin (U.S. Patent No. 6,900,235).

In levying the final rejection of the appealed claims, the Examiner has stated, *inter alia*:

> Agyin et al. disclose benzimidazole compounds for the treatment of cancers (Abstract; col. 2, line 39 to col. 3, line 61). The benzimidazole compounds are inhibitors of microtubules as recited in claim 22 (col. 25, lines 43-67; Table 5). The compounds of the invention are disclosed to be useful in combination therapy, such as by combining the benzimidazole compound with a chemotherapeutic agent and/or "potentiator" (col. 17, lines 1-60; col. 23, lines 29-31). A suitable potentiator is suramin as recited in claim 22 (col. 17, lines 56-57).
>
> January 5, 2009 Office action, p. 4 third paragraph.

Argument

Appellants respectfully disagree with the final rejection, because, as explained below, Agyin does not teach a suramin combination, and does not teach suramin as a potentiator. Therefore, Agyin does not teach appealed claim 22 and by definition all claims dependent therefrom.

None of Agyin's compounds have antitumor activity in animals bearing transplanted tumors.

Agyin provided limited data to support enablement for the treatment of cancers. Cytotoxicity data was presented for 43 benzimidazole compounds and showed IC_{50} concentrations ranging from <10 nM (3 compounds), to >100 μM (6 compounds) (table 4), but none of the compounds tested showed *in vivo* antitumor effect at the highest dose tested (Table 6). As indicated in column 27, line 21, a treatment that causes an increase in lifespan of less than 25% (T/C<125%) is defined as a no activity treatment. All compounds tested showed no activity, except for compound 3-1, which has a T/C value of 132% in one of the four dose levels tested, *i.e.*, 50 mg/kg i.p. However, the other three dose levels, including a higher dose level of 100 mg/kg,i.p., showed inactive T/C values of 97%, 98%, and 108%.

No enablement of combinations of benzimidazole compounds with other compounds, such as chemotherapeutic agents or "potentiators", was provided. It is generally known that drugs, which show activity in cultured tumor cells *in vitro*, frequently do not have antitumor activity in animals or human patients. It also is well known that compounds, which are inactive in animal models, are unlikely to be active in human patients. Furthermore, it is unlikely to receive regulatory approval for testing in humans a drug that is without activity in animal models. Therefore, an artisan will not be motivated to use the compounds of Agyin's invention, either singly or in combination, and Agyin does not teach the use of any form of combination therapy.

Agyin does not teach a suramin combination.

Agyin proposes to use the benzimidazoles in combination with any chemotherapy agent (column 12, ll. 51-54: "Chemotherapeutic agents used in combination with a compound of the present invention or salt thereof may be selected from any of these groups but are not limited thereto."), or with chemotherapeutic agents and/or potentiators (column 23, ll. 29-32), listing at least 91 compounds as possible "potentiators" (column 17, ll. 1-64). One of the listed compounds is suramin. The number of possible combinations proposed by Agyin, then, is at

least (43 * >100 * >91 =) >391,300, where 43 is the number of presented benzimidazole compounds, >100 is the number of chemotherapeutic agents, and >91 is the number of "potentiators" listed. Agyin does not provide the rationale for choosing one combination over the other 390,000+ combinations. Hence, Agyin's proposal to use benzimidazole combinations is merely an invitation to the artisan to search for a possible effective combination from among more than 390,000 possibilities. Accordingly, an artisan would not know which of the >390,000 combinations to study. Even with the teaching of using carboplatin as the cytotoxic to be combined with any one of the 91 potentiators and any one of the 43 benzimidazole compounds, the number of possible combinations is still >3,913, which is still a daunting number that would require substantial and burdensome experimentation.

Furthermore, it is well known in the art that there is only a vanishingly small chance of finding a synergistic drug combination, if the search process is a simple random testing of combinations of agents. Hence, an artisan would not be motivated to randomly test combinations. In short, Agyin's disclosure lacks specific and functional steps to enable an artisan to practice Agyin's invention. In fact, an artisan would be **discouraged** in using Agyin's teaching, since (a) the benzimidazole compounds are inactive in animal studies, (b) no data on possible synergy of any of the combinations is provided, and (c) no other indicators or rationales suggesting a beneficial effect of a combination with benzimidazole compounds were provided. Finally, since Agyin does not teach any combination, he also does not teach a particular combination containing suramin.

Agyin does not teach using suramin as a potentiator.

Agyin does not teach using suramin as a potentiator for at least two reasons. First, Applicants have shown that the potentiator effect of suramin happens only at low concentrations (U.S. Patent No. 6,599,912). Suramin does **not** have sensitization effect at high dose. This shows that the dose is critical to enablement of using suramin. Because Agyin failed to provide the important enablement of the dose requirement, he does not teach using suramin as a potentiator.

Second, Agyin does not teach how to obtain the narrow concentration range of 10 to 50 μM maintained over 48 hours that would offer the sensitization effect. As described in the appealed application, development of the nomogram for finding the proper suramin dose required many innovative steps and extensive research including experimentation in human

patients. Hence, a person with ordinary skills would not be able to combine suramin with the benzimidazole compounds.

The Examiner states (page 4, third ¶): "With regard to claim 26, Agyin et al. teach that carboplatin is a chemotherapeutic agent that may be combined with the disclosed anti-microtubule compounds (Table 3A) and that the compounds of the invention can be combined with chemotherapeutic agents and/or potentiators to provide combination therapy (col. 23, lines 29-31). Accordingly, addition of both suramin and carboplatin to a kit comprising an anti-microtubule compound as disclosed in Agyin et al. would have been obvious to one skilled in the art at the time the invention was made." Appellants respectfully disagree, for the following reasons.

Agyin's benzimidazole compounds are not antimicrotubule compounds. As described in Agyin (column 13 l. 39, bridging to column 14, l. 5), tubulin interactive agents act by binding to specific sites on tubulin, inhibiting the formation of microtubules. Microtubules are critical cell structure units. Therefore, anti-tubulin or anti-microtubule agents kill the cell by inhibiting microtubule formation. However, the benzimidazole compounds described in Agyin are not anti-microtubule compounds, for the following reasons. First, the compounds had little activity against microtubule, showing at most mild (≤50%) microtubule inhibition at 2 μM concentration (table 5). Second, a well known pharmacological principle on drug action mechanisms is the cause-and-effect relationship. In other words, if a drug acts by inhibiting a target X, then the inhibition of X is correlated with the treatment outcome. In the case of an anti-microtubule, its inhibition of microtubule formation should correlate with its cytotoxicity. But such correlation is not found for benzimidazole compounds; a comparison of the data in table 4 and 5 shows that, *e.g.*, two of the compounds that had no microtubule inhibition (3-9, 3-10) showed cytotoxicity at IC_{50} values of less than 1 μM, whereas the only compound causing 50% inhibition of tubulin polymerization (2-12) did not exhibit cytotoxicity. The weak microtubule inhibition and the lack of correlation between the microtubule inhibition and cytotoxicity indicate that the benzimidazole compounds are generally not anti-microtubule agents.

Applicants' claim 22, from which claim 26 depends, includes: "a cytotoxic agent being one or more of an anti-microtubule agent ...". However, as shown above, the benzimidazole compounds are **not** anti-microtubule agents. As further shown above, Agyin did not teach any combinations, including combinations with suramin. Furthermore, as shown below, Agyin did not teach kits containing combinations of agents.

Agyin does not teach using kits containing combinations of agents.

The Examiner proposes that Agyin's teaching of possible combinations of chemotherapeutic agents and potentiators with anti-microtubule compounds of the appealed claims would make the kit of claim 26 obvious to one skilled in the art at the time the invention was made. Appellants respectfully disagree with this point of view for several reasons. First, Agyin does not propose kits containing combinations of agents (column 24, ll. 6-22; claim 14). He only proposes kits containing a therapeutically effective amount of a benzimidazole. All other components of the kit are optional, and the list of optional components does not include chemotherapeutic agents or potentiators. Therefore, Agyin does **not** teach kits containing combinations of agents, and certainly not a kit containing a chemotherapeutic agent, suramin, and the instructions as needed to make suramin effective as sensitizer or potentiator of the action of the chemotherapeutic agent.

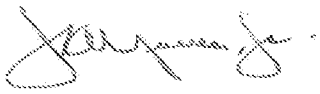
Second, claim 26 is merely an example of a possible formulation of claim 22 and is dependent of this claim. Therefore, allowance of claim 22 should automatically lead to allowance of claim 26 and the objection is moot.

Third, the instant disclosure is a nomogram that is required to enable the use of the kit containing suramin, which is used to improve the activity of one or more cytotoxic agents, also contained in the kit. The inventive element of instructions that enable application of medicaments, and that provide a functional relationship between the printed matter (instructions) and the claimed kit, is totally lacking in Agyin. His disclosure pertains to a number of compounds of which the utility has not been clearly proven, in spite of his claims to be effective in the treatment of various diseases. In the remainder of his disclosure, he merely postulates that the utility of his compounds could be increased when used in combination with other compounds. This speculation appears grounded in the widely accepted rule in treatment development for cancer and viral diseases that the most effective therapies for these diseases frequently are combination therapies. This postulated utility, however, in no way anticipates the utility of the nomogram developed for the use of suramin as a sensitizer in the treatment of patients with cancer, and the utility of kits containing the nomogram, suramin, and the chemotherapeutic. As a result, Agyin does not render the appealed claims obvious.

Conclusion

Accordingly, Appellants respectfully urge the Board to overrule the rejection of the appealed claims and to permit the appealed application to pass to issue.

Respectfully submitted,



Date: 26 August 2009

Jerry K. Mueller, Jr.
Reg. No. 27,576
MUELLER SMITH & OKULEY, LLC
Mueller-Smith Building
7700 Rivers Edge Drive
Columbus, Ohio 43235-1355
tel.: 614-436-0600
fax: 614-436-0057
email: *smueller@muellersmith.com*

CLAIMS APPENDIX

The Appealed Claims

Claim 22. A kit for carrying out the combined administration of suramin with one or more cytotoxic agents, comprising:

(a) suramin formulated in a pharmaceutical carrier;

(b) a cytotoxic agent being one or more of an anti-microtubule agent, a topoisomerase I inhibitor, a topoisomerase II inhibitor, an anti-metabolite, a mitotic inhibitor, an alkylating agent, an intercalating agent, an agent capable of interfering with a signal transduction pathway, an agent that promotes one or more of apoptosis or necrosis, an interferon, an interleukin, or a tumor necrosis factor; and

(c) instructions for therapeutic use of said suramin in combination with said cytotoxic agent(s) in one or more of inhibiting growth, proliferation of tumor cells, or inducing killing of tumor cells, calling for:

(i) administering suramin in a required dose to establish a low circulating concentration of suramin in said patient of below about 200 μM; and

(ii) administering said chemotherapeutic agent to said patient when said low circulating concentration of suramin of below about 200 μM is present in said patient,

wherein the required dose of suramin is determined in step (c) by the steps of:

(c1) determining the squared value of the body surface area (BSA) of said patient;

(c2) determining the time elapsed, in days, since the initiation of the last suramin treatment; and

(c3) calculating the dose of low dose suramin using a nomogram that shows the dose according to the parameters of squared value of body surface, and elapsed days since last suramin treatment,

said nomogram comprising:

Nomogram For Calculating Suramin Dose

Cycle 1*	125
Days since the administration of the first dose of previous cycle	FACTOR
7	39
8	43
9	47

10	51
11	55
12	58
13	61
14	64
15	67
16	69
17	72
18	74
19	76
20	78
21	80
22	82
23	84
24	86
25	87
26	88
27	90
28	91
29	92
30	93
31	94
32	95
33	96
34	97
35	98
36	98

37	99
38	100
39	100
41	102
42	102
44	103
47	104
49	105
52	106
55	106

where:

$$\text{First cycle dose } \_\text{mg}\_ = \frac{\_21.4*5.13*\text{BSA}^2\_}{e^{-\_0.0026 \text{ or } 0.0022*48\_}} = 125*\text{BSA}^2 \qquad \text{Eq. 15}$$

and

Subsequent cycle dose (mg) = First dose * (1- $e^{-k^* t}$) = $125*\text{BSA}^{2*}$ (1- $e^{-k^* t}$) = $\text{FACTOR}*\text{BSA}^2$ Eq. 16

wherein

"BSA" is body surface area in units of m^2,

"k" is the rate constant of decline of suramin concentrations in plasma in units of 1/hour,

"t" is time after suramin administration in units of hours.

Claim 26. The kit of claim 22, wherein one of the cytotoxic agents is one or more of carboplatin, paclitaxel, docetaxel, gemcitabine, or 5-fluorouracil.

Claim 27. The kit of claim 22, wherein said low circulating concentration of suramin is between about 10 and 200 μM.

Claim 28. The kit of claim 27, wherein said low dose of circulating suramin is between about 10 and 50 μM.

Claim 32. The kit of claim 22, wherein a suramin dose is administered such that a concentration of between about 10 to about 50 μM over 48 hours is achieved in a patient.

Claim 33. The kit of claim 22, wherein two-thirds of the therapeutically effective amount of suramin is given on the first day and the remaining one-third of the therapeutically effective amount of suramin is given about 24 hours later.

Claim 34. The kit of claim 22, wherein a suramin dose greater than a low dose suramin is administered to a patient and a chemotherapeutic agent thereafter is administered to said patient only after a suramin plasma concentration of between about 10 to about 50 μM is achieved in said patient.

EVIDENCE APPENDIX

March 6, 2008 Declaration of Jessie L.-S. Au

RELATED PROCEEDINGS APPENDIX

None.